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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/990,046

11/20/2001

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EXAMINER

HOWARD, ZACHARY C

ART UNIT

PAPER NUMBER

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/990,046	Applicant(s) DE SAUVAGE ET AL.	
	Examiner Zachary C. Howard	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 29,30,36-40,46-49 and 52-54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 29,30,36-40,46-49 and 52-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 March 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/15/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 8/22/07 has been entered in full. Claims 29, 30, 39, 40 and 49 are amended. (Claims 1-28, 31-35, 41-45, 50 and 51 were previously canceled). No new claims are added.

Claims 29, 30, 36-40, 46-49 and 52-54 are pending in the application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (12/22/06).

The objections at pg 3 to claims 29, 30 and 40 are *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 49 under 35 U.S.C. § 112, first paragraph at pg 3-4 for failing to provide enablement for deposit of ATCC 209779 is *withdrawn* in view of Applicants' amendments to said claim to instead refer to ATCC 209778.

The following grounds of rejection of the claims under 35 U.S.C § 112, 2nd paragraph, are *withdrawn* in view of Applicants' amendments to the claims:

The recitation of "binds to hedgehog polypeptide" in claim 29 (pg 6).

The recitation of "variant thereof in claims 29 and 39 (pg 6).

The recitation of "about" in claims 29 and 39.

It is noted that the claims remain rejected under 35 U.S.C. § 112, 2nd paragraph, for the reasons set forth below.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly

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claim the subject matter which applicant regards as the invention. This rejection was maintained at pg 4-7 of the 12/22/07 Office Action.

It is noted that independent claims 49 and dependent claims 52-54 were inadvertently left out of the statement of rejection at pg 4 of the 12/22/06 Office Action. However, the rejection also states, "The term "specifically" in claims 29, 39, and 49 is a relative term which renders the claim indefinite". The rejection concludes "[t]he remaining claims are rejected for depending from an indefinite claim". Furthermore, claims 49 and 52-54 were included (under the same grounds of rejection) in the rejection under 35 U.S.C. § 112, second paragraph, set forth in the preceding Office Action (4/5/06). As such, claims 49 and 52-54 are considered to have been included in the rejection under 112, 2nd paragraph in the 12/22/06 Office Action.

As set forth previously, the term "specifically" in claims 29, 39 and 49 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The genus of proteins bound by the claimed antibody is rendered indefinite by the use of "specifically". The remaining claims are rejected for depending from an indefinite claim.

Applicants' arguments (8/22/07; pg 4-5) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants point to page 146 of the reference Burry (2000) as providing "compelling evidence that the art recognizes that an antibody that "specifically binds" means one that uniquely binds to the identified antigen" (pg 5). Applicants argue that Burry describes antibody specificity as being "largely determined by the method of production, the most important of which include purification with the immunizing peptide" and argue that this supports that "immunoprecipitation is a suitable manner, if not preferred manner of determining antibody binding specificity."

Applicants' arguments have been fully considered but are not found persuasive. As set forth previously, the term "specifically binds" is not defined in the instant application and the specification does not clearly define what is included or excluded by

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the term. Applicants argue that the term “specifically binds” with respect to an antibody is defined in the relevant art as referring to an antibody that binds solely to one antigen and not to any other antigen; in support Applicants point to Burry (2000). It is acknowledged that the definition set forth by Applicants could be used in the art as a definition of “specifically binds”; however, it is maintained (as set forth previously in the 12/22/06 Office Action at pg 5) that an antibody that binds to an identical epitope that is found within two otherwise different proteins could also be considered to be specific for these two proteins and non-specific for other proteins. The reference of Burry (2000) has been fully considered but is not sufficient to demonstrate that the term “specifically binds” as used in the relevant art has the defined meaning put forth by Applicants. The statement in Burry that “[t]he characterization of antibody specificity requires demonstration that the antibody binds only to the protein that contained the immunogen peptide” does not exclude multiple proteins that contain the same immunogen peptide (e.g. closely related proteins containing largely identical stretches of amino acids). Furthermore, the relevant art also teaches that antibody specificity is not clearly defined in the relevant art. For example, Van Regenmortel (1998) teaches “[a]lthough the concept of specificity is widely used in biology, few authors have attempted to define it” (pg 37 of Van Regenmortel. 1998. *Journal of Immunological Methods*. 216: 37-48). Van Regenmortel (1998) further teaches, “[a]ntibody specificity is a ternary relational property which refers to the antibody’s capacity to discriminate between two or more epitopes” (see Abstract). This supports that the term “specifically binds” can refer to the ability of an antibody to distinguish two different epitopes rather than two different antigens. As shown in Figure 1 of Van Regenmortel, the same antibody (“anti a”) binds to the same epitope (“a”) on two different antigens (“Antigen 1” and “Antigen 2”). Thus, the “anti a” antibody “specifically binds” to epitope “a” and not to other epitopes, despite the fact that it binds to multiple proteins that contain the same epitope. Van Regenmortel states, “[o]ne type of cross-reactivity, more properly called shared reactivity, arises when a particular antibody recognizes the same epitope in two different multideterminant proteins. This corresponds to the absolute specificity Ehrlich had in mind since the antibody then reacts in an identical fashion with the same

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complementary epitope present in the two antigens" (pg 42). In summary, the relevant art supports that the term "specifically binds" as used in the instant claims and specification is (1) undefined and (2) can be used to refer to an antibody that binds to the same epitope in different proteins.

Applicants are advised that the instant rejection with respect to "specifically binds" was made final because the same claims were maintained as rejected on the same grounds that have been of record. However, the new reference of Van Regenmortel (1998) has been cited as evidence supporting this portion of the rejection, and in response to Applicants' arguments. Applicants may submit counter-evidence in response to of Van Regenmortel (1998), which will appropriately be entered after final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al. (18 February 1998. Nat Genet. 18(2): 104-6) in view of Tso et al (U.S. Patent No. 5,932,448, published 3 August 1999, and filed 11/29/1991). This rejection was maintained at pg 7-9 of the 12/22/06 Office Action.

Applicants' arguments (8/22/07; pg 5-6) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that Motoyama does not teach "polypeptides having the requisite degree of identity (at least 95%) to SEQ ID NO: 2". Applicants further argue that neither reference alone or in combination suggests antibodies that bind only to SEQ ID NO: 2 ("specifically bind").

Applicants' arguments have been fully considered but are not found persuasive. As set forth above, in the section titled "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the term "specifically binds" has been interpreted to read upon antibodies

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that bind to a specific epitope and not to other epitopes, even if the specific epitope is found in multiple proteins. Therefore, the Examiner maintains that the teachings of Motoyama in view of Tso render obvious antibodies that specifically bind to instant SEQ ID NO: 2.

As amended, claims 29, 30, 39, 40 and 49 each encompass a monoclonal antibody that specifically binds to a patched-2 polypeptide of instant SEQ ID NO: 2, or variants of SEQ ID NO: 2 that are at least 95% identical and bind to a *hedgehog* or *Smoothened* polypeptide. The remaining claims depend from claims 29, 39 or 49 and limit the antibodies to those that are humanized (claims 36, 46 and 52), bispecific (claims 37, 47 and 53), or heteroconjugated (claims 38, 48 and 54).

Motoyama teaches the mouse gene *Ptch2* that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID NO: 2 (which is the human patched-2 polypeptide). An alignment of the two sequences was attached to the 7/12/05 Office Action as Sequence Alignment #1. Motoyama does not teach an antibody to the mouse patched-2 polypeptide.

Tso teaches general methods for producing bispecific antibodies (col 1, line 62-67). Tso further teaches monoclonal antibodies for use in production of bispecific antibodies (col 7, line 19). Tso further teaches humanized antibodies for use in bispecific antibodies (col 2, lines 46-47). The instant specification defines heteroconjugated antibodies as "antibodies composed of two covalently joined antibodies (pg 26). Tso teaches chemical cross-linking of two antibodies to produce a bispecific antibody (col 1, lines 34-35). This bispecific antibody taught by Tso meets the definition of a "heteroconjugated" antibody as defined by the specification.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make antibodies as taught by Tso to the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would be motivated to do so because Tso teaches that the antibodies have general uses applicable for use with any protein, such as cross-linking a horseradish peroxidase for purposes of detection (see col 11, lines 52-55). The person of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse

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patched-2 polypeptide, and Tso teaches the methods necessary to produce antibodies to any protein sequence.

Such antibodies are encompassed by the instant claims for the following reasons. Due to the high degree of similarity between the two sequences, including numerous regions of 20 or more amino acids with 100% identity between the sequences, one of skill in the art would reasonably predict that numerous monoclonal antibodies (including bispecific, humanized, or heteroconjugated antibodies) made to mouse patched-2 polypeptide as taught by Motoyama would specifically bind to the human patched-2 polypeptide of instant SEQ ID NO: 2. The regions of exact identity contain epitopes that generate monoclonal antibodies that would bind to either protein, particularly if the proteins are denatured and presented in linear form. As set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the term "specifically binds" is not clearly defined in the specification as excluding antibodies that bind to the same epitope in other proteins (e.g., mouse patched-2). Therefore, as many of the monoclonal antibodies to mouse patched-2 would also bind to instant SEQ ID NO: 2, the teachings of Motoyama in view of Tso render obvious the antibodies encompassed instant claims.

Conclusion

No claims are allowed.

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THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646